Video Article

Quantitative Assessment of Cortical Auditory-tactile Processing in Children with Disabilities

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Abstract

Objective and easy measurement of sensory processing is extremely difficult in nonverbal or vulnerable pediatric patients. We developed a new methodology to quantitatively assess children's cortical processing of light touch, speech sounds and the multisensory processing of the 2 stimuli, without requiring active subject participation or causing children discomfort. To accomplish this we developed a dual channel, time and strength calibrated air puff stimulator that allows both tactile stimulation and sham control. We combined this with the use of event-related potential methodology to allow for high temporal resolution of signals from the primary and secondary somatosensory cortices as well as higher order processing. This methodology also allowed us to measure a multisensory response to auditory-tactile stimulation.

Video Link

The video component of this article can be found at http://www.jove.com/video/51054/

Introduction

The study of developing cortical sensory processes is essential to understanding the basis for most higher order functions. Sensory experiences are responsible for much of the brain's organization through infancy and childhood, laying the foundation for complex processes such as cognition, communication, and motor development[1-3]. Most pediatric studies of sensory processes focus on auditory and visual domains, mainly because these stimuli are easiest to develop, standardize, and test. However, tactile processing is of particular interest in infants and children as it is the first sense to develop in the fetus[4,5], and somatosensory information is integral to the function of other cortical systems (*e.g.* motor, memory, associative learning, limbic)[6]. Current methods assessing somatosensory processing are limited by the choice of tactile stimulus. A common choice is direct electrical median nerve stimulation[7,8], with the potential for discomfort. Other effective methods use active tasks such as discrimination, recognition, and localization of stimuli, requiring both attention and high levels of comprehension[9]. All of these methods are therefore limited in their use in young children and infants.

Therefore, our goal was to develop a tactile paradigm that addresses these limitations by being noninvasive and reducing the need for a subject's active participation. Additionally, it needed to have a standardized level of stimulation and a sham-control. For this we developed the "puffer" system, a dual-channel, timed, and calibrated air-puff delivery system, allowing us to measure the effects of light touch in infants and other vulnerable populations.

Functional MRI studies showed that stimulation by puffs of air activates sensory cortices, although the length and challenges of such studies, such as immobilization, lengthy sessions, and anxiety-provoking settings make them difficult to perform in young children. Therefore, we combined our novel delivery system with Event-Related Potential (ERP) methodology in order to provide temporal resolution of sensory processing of light touch in a brief, child-friendly testing session.

This new paradigm offers the needed flexibility to study sensory processing in diverse populations, ages and clinical settings. It also has the advantage of being compatible with auditory stimuli, allowing for multisensory assessments. Until now, accurate and reliable tactile assessment has not been possible in infants or in children who are unable to reliably respond due to intellectual/language disorders. This methodology aims to fill this gap in order to aid in early identification of sensory processing deficits and intervention during a period of maximal brain plasticity. Improvements in sensory processing in infancy may influence the cascade of neurodevelopmental

The following procedures are all included in Vanderbilt Institutional Review Board approved protocols.

Protocol

1. Assessment of Response to Light Touch

1. Place the electrode net (*e.g.* 128-channels geodesic sensor net) on child or infant's head. Adjust sensors for full contact using warm saline solution. If on a child, ensure child is sitting comfortably in parent or caregiver lap. If on an infant, ensure that infant is lightly swaddled and either held in caregiver's arms or in a supine position in an open crib.
2. Position a 1 mm nozzle 0.5 cm below the tip of the index finger of the tested hand. Place finger for a young child or palm for an infant in a mold holder and secure with Velcro tape proximal and distal to joint to ensure consistent distance from nozzle to the finger or hand. It is absolutely essential that the child maintains the proper finger position throughout the testing session. Ensure this by periodically assessing finger and hand placement and having child with caregiver if young. If testing an infant, stop protocol if infant cries and provide comfort before restarting. If testing young child, ask caregiver to provide comfort and reassurance throughout the short testing period.
3. Start air compressor at 40 psi through regulator to supply valve inputs for tactile stimuli.
4. Run stimulus delivery program.
    1. For the tested hand, present 60 puff stimuli randomly interspersed with 60 sham trials (an air puff delivered via a separate nozzle pointed away from the finger).
    2. Do not present more than two repetitions of a puff or sham in a row. Vary the inter-trial intervals randomly between 2,000-2,500 msec. The purpose of this is to reduce habituation, where a stimulus is no longer perceived. The total time for a sequence of 120 trials should be 4.5-5 min.
    3. Run the identical protocol again for the other hand if studying asymmetrical somatosensory disorders.
5. For protocols not requiring attention to stimulus no further set up is needed. This applies to infant testing. For enhancement of attention in young children (which results in larger specific ERP peaks in recording), provide a task.
    1. Task example for 5-year-olds: Describe air puffs as "bubbles" blown by "fish" in a "fish tank" (a decorated box concealing the puffer apparatus). Ask children to guess whether each "bubble" is delivered by a blue or a red "fish". Tell the child that they do not need to and should not say anything while they are performing this task (see set up with mock aquarium in **Figure 1**).

2. Assessment of Response to Multisensory Protocol (Auditory-tactile Simultaneous vs. Summed Individual Responses)

1. Run through steps 1.1-1.3 as described above. Stimuli are described in **Table 1**.
2. Run the stimulus delivery program (*e.g.* in E-Prime software). For the tested hand, an auditory-tactile paradigm can present the following 4 stimuli randomly, with 60 trials/ stimulus: puff , puff-/ga/, /ga/-sham, sham. Again, to limit the possibility of habituation, do not present more than two repetitions of a puff or sham in a row in any condition, and vary the inter-trial intervals randomly between 2,000-2,500 msec. Each sequence of 240 trials should take between 9-10 min.
3. Run identical protocol over for the other hand.
4. Provide a soundless age-appropriate cartoon at initiation of protocol and continue it throughout the procedure to prevent increase in motor artifacts from restlessness, and to decrease the background from large patient-generated delta waves when they are bored. For example, in 5-year olds, we used a loop of 20 min of a purchased video, played on mute and restarted before each subject was tested. No attention to stimulus is needed, therefore the looped cartoon provides a visual background disconnected from the stimuli.

3. Software and Equipment Set Up

1. To program the software, set up two serial commands sent by the stimulus control application. One identifies the puff, the other the sham. Have the stimulus control application send the commands to a microcontroller.
2. Have the microcontroller generate a TTL pulse (*e.g.* 20 msec duration) to the corresponding digital output channel. This output must be split into two lines, one for the digital input to the EEG recording system and one to the solenoid-gated air valves. Mark the opening of both valves in the EEG data stream.
3. Measure the pulse to puff latency for both real and sham conditions with an oscilloscope and a microphone. These should be uniform, and in the order of 10-15 msec. Adjust for the latency post-recording.
4. Calculate the force exerted at the nozzle in PSI using a manometer and by measuring the nozzle diameter. Use the formula F(N) = Pressure*Area. For example, the force exerted from a 1 mm radius nozzle at 6 psi yields F(N) = 0.03 lbs.
5. To modify the control application for the multisensory protocol, send two serial commands identifying a real puff or sham to the microcontroller as well as a recorded speech sound or silence. Note: In our paradigm we have used the computer generated, accent-neutral /ga/ sound, among others such as /da/, /du/, /bu/, *etc*.
6. Present auditory stimuli through a speaker placed at midline, 2 ft in front of the subject.
7. Align the sound onset timing to be simultaneous with the onset of the puff or with the delay measured in step 3.3, depending on which condition is desirable to the tester.

4. Data Acquisition and Preparation

1. Choose filters and references settings to sample data based on standard ERP methodologies. Here, use a 1,000 Hz with filters set to 0.1-400 Hz. During data collection, refer all electrodes to Cz and rereferenced them offline to an average reference.

2. To segment the data, filter the recorded data with desired filters and segmenting. For this study use a 0.3-40 Hz bandpass filter and segment the ongoing EEG based on the stimulus onset to include a 200 msec prestimulus baseline and a 500 msec post-stimulus interval.
3. Perform quality control of the data. Screen each segment for motor and ocular artifacts such as high frequency muscle activity, using computer algorithms included in the ERP software. Follow this screen by a manual review.
4. The automated screening criteria are set as follows in this protocol but can be modified: for eye channels, voltage >140 μV = eye blink and voltage >55 μV = eye movements.
5. Correct data from contaminated trials using an ocular artifact correction tool. Note: Any channel with voltage >200 μV is considered of poor quality. If >15 channels are of poor quality, we chose to discard the entire trial for reproducibility reasons.
6. Average ERPs. Rereference them to an average reference and then perform baseline-correction based on criteria chosen in step 4.2. Extract mean amplitude and peak latencies for various peaks, extrapolated from grand average waveforms of predefined populations. Note: In our case, we based the following on established literature of older children's response to median nerve stimulation[10-14]. We used P50 (30-80 msec), N70 (50-100 msec), P100 (80-150 msec), N140 (130-230 msec), and P2 (250-350 msec) peaks.
7. Include only data from electrodes overlapping preset locations (**Figure 2**). Derive data for individual electrodes and average within each cluster.

Representative Results

Assessment of light touch (Figure 3):

Characteristics of the cortical response to tactile stimulation using the Puffer system: The patterns of peaks in response to the puff are very similar to the cortical responses obtained using median nerve stimulation in normal adults[10,11]. The *early response (P50, N70, P100 peaks)* primarily reflects activity in the primary sensory cortex[12] and does not require awareness of stimulation. The *secondary response (N140 peak)* primarily reflects activity in the secondary sensory cortex and awareness of a somatosensory stimulus as has been documented in published studies[13,14]. This peak in our paradigm reflects processes in the secondary sensory cortex, modulated by attention to touch (the 'fish blowing bubbles task'). The *late response (P2 peak)* primarily reflects the beginning of cognitive neural activity related to sensory stimulation. This peak may reflect subjective attention to touch and involuntary orientation[15,16].

Puff vs. sham: Even though the sham presents a nonspecific tone-like sound at less than 35 dB, it cannot be considered completely inaudible[17], and therefore constituted an appropriate sham control. The sham is the sound of the air puff without the sensation of the puff, and therefore cortical responses for such trials are small at left and right central locations optimal for detection of tactile SEPs. Sham trials produced early low amplitude responses under all conditions, different from the tactile stimulation and consistent with tone-like auditory stimuli. Specifically, analysis of peak amplitudes showed a measurable difference between sham and air puff for P50 (mean amplitude difference ($D = -2.8$ mV 2.7, $p = 0.04$), N70 ($D = -3.9$ mV 4.0, $p = 0.04$) and N140 ($D = -4.1$ mV 3.5, $p = 0.02$).

Differences between affected vs. unaffected hand puffer responses in children with hemiparetic cerebral palsy (see **Table 2**, modified from *J. Child Neurology*[18]). As a proof of concept for the Puffer system, statistical analysis was performed on peak amplitudes and latencies to characterize differences upon stimulation of the affected hand compared to the unaffected hand. While the subject population was small ($N = 8$), significant differences were observed between the two hands.

Assessment of response to multisensory protocol: auditory-tactile simultaneous vs. summed individual responses (Figure 4)

To determine the effects of multisensory interactions associated with the simultaneous tactile (puff) and auditory (speech sound) presentation it is essential to compare the observed brain response to the algebraic sum of the responses to auditory and tactile stimulation presented separately. This analysis principle has been well documented in audio-visual studies[19-21]. In this case, the sham-sound condition and the puff alone condition are added, as a coupled sham - speech-sound allows us to account for low amplitude nonspecific auditory responses demonstrated in **Figure 1**. Because auditory-tactile multisensory effects are typically evident in the early phases of cortical responses[21], we focused our observation on the 0-140 msec time window. Two positive calculated peaks are observed, corresponding to the P50 (30-80 msec) and P100 (80-150 msec). Immediately after this, a large negative deflection can be observed, most likely corresponding to the N140 (130-230 msec).

In a second study of 10 children (ages 5-8) (**Figure 4**), the true multisensory response to auditory-tactile condition can be observed to have differences in all three deflections. The difference between the amplitude of the summed and multisensory mean amplitudes represents the contributions of multisensory neural processes to individual sensory responses. The existence of a multisensory auditory-tactile response to a speech sound-air puff stimulus had been suggested in adults by using neurobehavioral measures[22] and this ERP methodology appears to confirm its existence in children as well, but at the level of cortical processing.

ERP Peaks	Characteristics of response	P for affected vs unaffected
P50 and N70	No statistical difference between affected and unaffected hand stimulation	NS
N140	↑ amplitude in affected	0.036
	compared to unaffected hand stimulation	
P2	↓ amplitude ipsilateral and ↑ contralateral in affected	0.046
	compared to unaffected hand stimulation	
	↑ latency ipsilateral in affected hand only	0.005
	compared to contralateral	

Table 1. Selection of stimuli for multisensory paradigm.

Sensory modality	Stimulus type	Specific example
auditory	Speech sound	computer generated /ga/sound
	Nonspecific sound	tone-like sound generated by air puff
tactile	Light touch	calibrated air puff
auditory-tactile = multisensory	Simultaneous speech sound with touch	simultaneous /ga/and puff

Table 2. Comparison of puffer results for affected and unaffected hand in children with cerebral palsy (N =8).

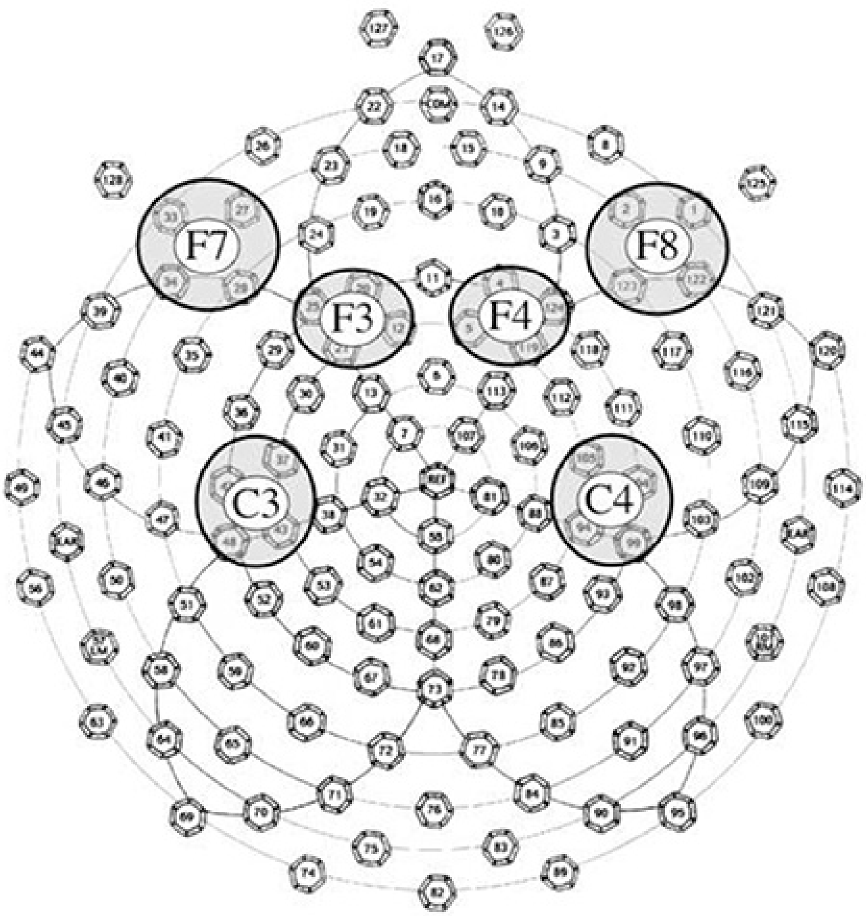

Figure 1. Electrode cluster representation on ERP net:

C : centroparietal

F : frontal

Odd numbers correspond to left-sided locations

Even numbers correspond to right-sided locations

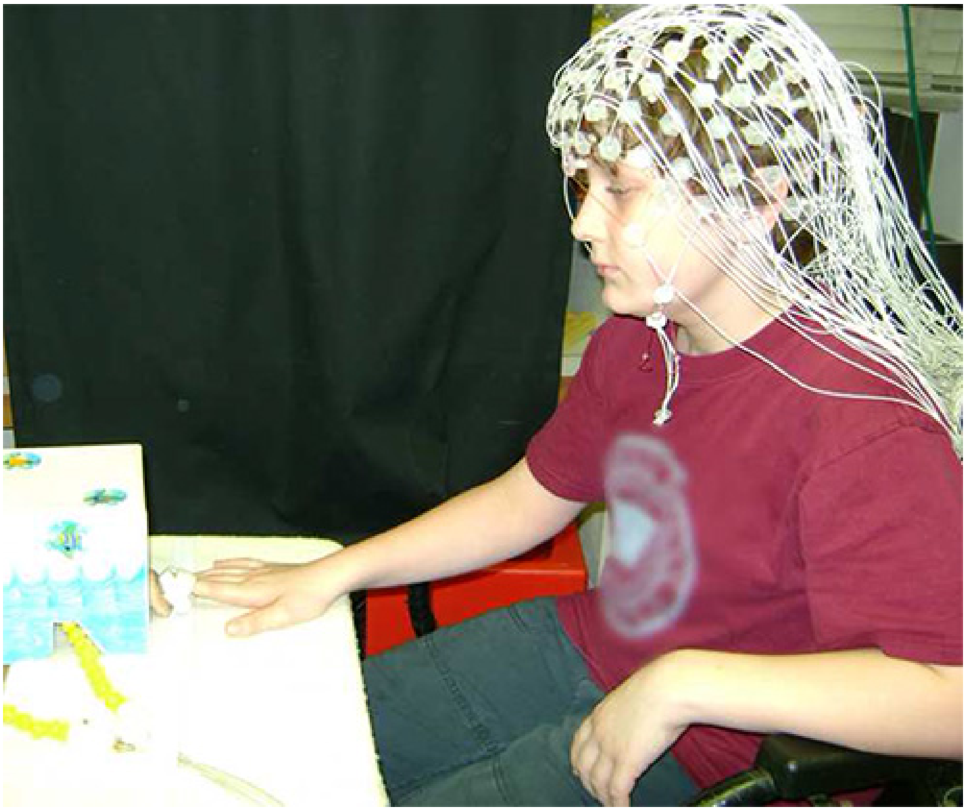

Figure 2. Child undergoing Multisensory Testing. Compressed air flows through yellow flexible nozzles through cardboard "aquarium box" and out into clay mold in which finger is secured. For sham puffs, compressed air flows through nozzle aimed in back of box. ERP net is in place and child can visualize his arm, surroundings, and the box.

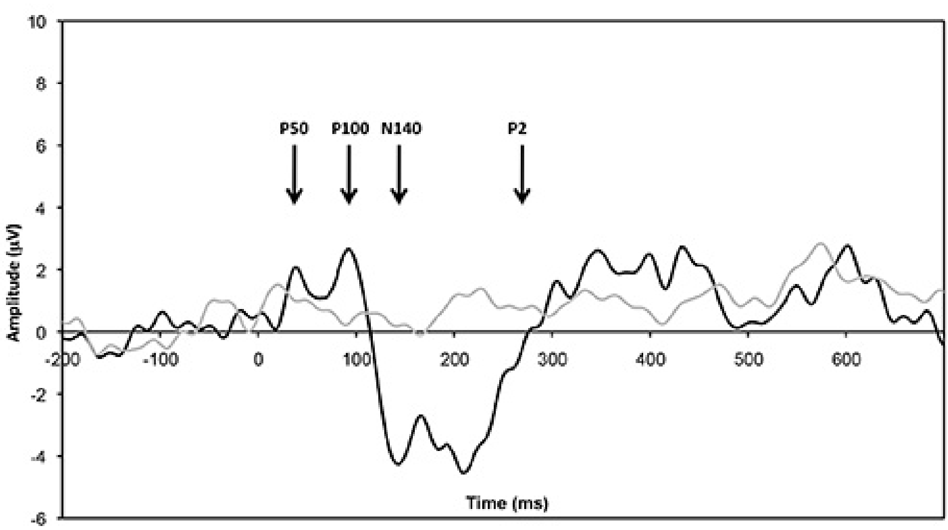

Figure 3. Comparison of responses to puff and sham control in the contralateral cortical side to stimulation of an affected hand. Tracings represent averages of N = 8 children (ages 5-8), centroparietal locations only. Black line represents puff, grey line represents sham response.

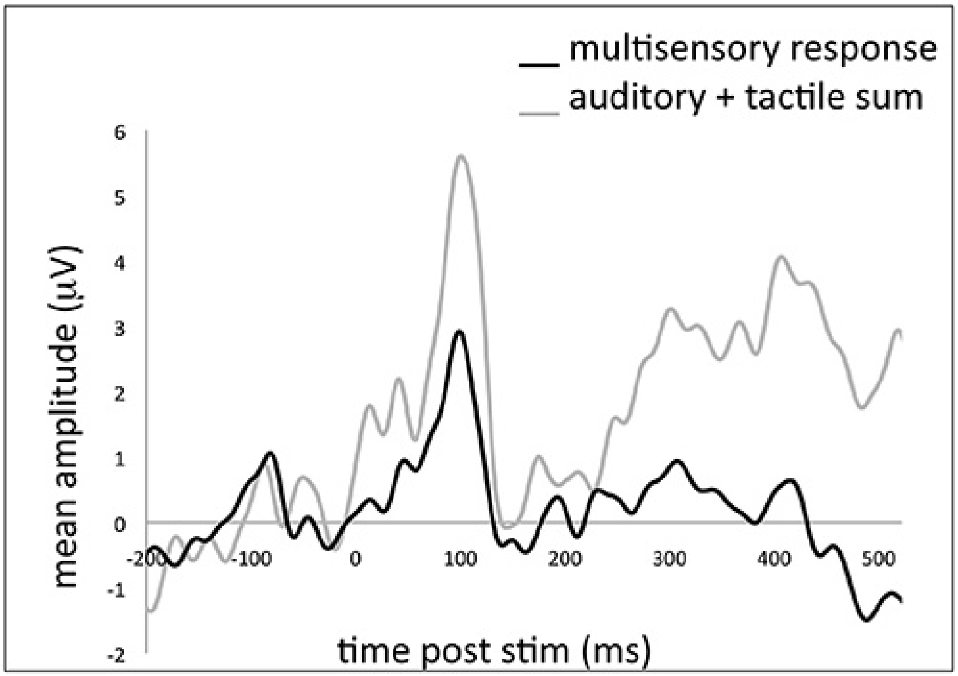

Figure 4. Responses recorded in somatosensory area of hemisphere contralateral to tactile stimulus, binaural auditory stimulus. Tracings represent averages of N = 10 children (ages 5-8)*, centroparietal locations only. Grey line represents calculated summed response of /ga/-sham + puff, black line represents true multisensory response of simultaneous /ga/-puff.

* This was a separate study from the one described in **Figure 3**, performed in 2012, also with Vanderbilt IRB-approved protocols.

Discussion

This novel combination of air puff and ERP (referred to as the "Puffer system") to measure cortical processing of light touch and tactile-auditory responses is well tolerated by young children with disabilities and by infants. This holds true for unisensory and multisensory versions, and whether the attentional component is added or not in the case of young children. The reasons for the success of this methodology in assessing a young and vulnerable population are due to both the use of an innocuous tactile stimulus as well as to the use of ERP methods and equipment. The tactile paradigm can be performed in a total of 5 min, while the multisensory paradigm takes 10 min. This is especially useful for assessment of toddlers or subjects with behavioral challenges. The stimulus itself can be calibrated to never exceed light touch or pressure, making tolerance a nonissue, in contrast to electrical nerve stimulation. Finally, the openness and flexibility of the measurement device, the commonplace surroundings and the lack of physical restraint create a reassuring and child-friendly setting for experiments. This holds true especially in infants who can be comforted by light swaddling and being held by a caregiver. Therefore this methodology has applications for patient populations throughout the spectrum of health and disease, as well as through the lifespan from infancy to older adulthood.

While these characteristics make the "Puffer system" easier to administer in young children than functional MRI, ERP does not provide the same degree of spatial resolution[24]. Caution should be used in attributing ERP signal sources to underlying structures, even in the case of well-studied somatosensory potentials[25]. This is especially relevant for children with large space-occupying brain lesions. However, the temporal resolution offered by the Puffer system equals that of direct median nerve stimulation in adults, in whom the cortical origins of various ERP peaks have been well characterized.

A critical step in this paradigm is the positioning of the nozzle in proximity to more densely innervated areas in order to achieve optimal ERP signal. Hands, feet and face are obvious choices due to their dense innervation and large sensory representations in the somatosensory cortex. The force of the compressed air may also be optimized, either through the compressor or through the modification of the nozzle diameter. Use of a manometer to calibrate the force at the level of the nozzle itself is recommended to ensure accuracy. Ensuring the proper positioning of the hand with a mold or armboard with Velcro straps will further ensure that the distance between the nozzle and the skin surface remains constant.

Caution should also be used in trying to further decrease the time for paradigm administration or increase the number of stimulus trials. Sixty trials are sufficient to generate a clear ERP signal and allow for some data loss due to artifacts but fewer trials may not produce reliable, reproducible data. Conversely, more trials per condition may improve the ERP signal strength but could also result in habituation to stimulations, or increased motor/ocular artifacts due to boredom.

Possible modifications built into the methodology are the study of attentional effects on stimuli. The stimulus is light enough not to require attention but this can easily be enhanced, resulting in increases in ERP amplitudes especially in the early peaks from P50 to N140. Also built-into the multisensory system are the addition of varied speech sounds and tones. The timing of auditory and tactile signals can also be modified to from simultaneous to staggered, to study the effects of one modality on another.

Applications being realized in the near future include wider extension of the paradigm to infants and newborns with brain injury or abnormal sensory experiences in the neonatal period such as intensive care hospitalization as well as adolescents with disabilities. The value of such testing can be both predictive of future sensory-motor limb function. It may also be indicative of the ability of children to process multiple sensory streams as connected inputs and be a measure of efficacy for therapies aimed at sensory integration. For adults, the force of the tactile stimulus may need to be increased to provide similar results. Finally, additions of visual stimuli to the multisensory model are in conceptual stages and will provide an invaluable objective tool for the measurement of sensory processing functions and disorders.

Disclosures

The authors declare that they have no competing financial interests.

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